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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/002,413	01/02/1998	RICHARD C. ALLEN	311772000500	7792

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EXAMINER

WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 12/12/2002

37

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/002,413

Applicant(s)

Allen et al.

Examiner

Michael C. Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Oct 7, 2002

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66, and 68-73 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66, and 68-73 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). 36

6) Other: _____

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-7-02, paper number 33, has been entered.

Applicant's arguments filed 10-7-02, paper number 35, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 43, 54, 55, 60, 61, 64 and 67 have been canceled. Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 are pending and under consideration in the instant application as they relate to a method of administering cells to create an immunologically privileged site as originally elected.

Claim Rejections - 35 USC § 112

1. Claim 66 remains rejected and claims 56, 57, 62, 63 and 70-73 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

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The limitation “wherein said RPE cells are allogenic to the mammal” (claim 66) does not have support in the specification as originally filed. While the specification contemplates administering non-RPE that are allogeneic to the host using RPE cells provide immune privilege and increase survival time of the non-RPE in the host (pg 7, line 8 and line 28), the specification does not contemplate administering RPE that are allogeneic to the host or to the non-RPE cells.

Applicants argue pg 7, lines 15-18, support the phrase because it states immunosuppression by an agent such as FasL would not cause an immunological attack against the transplanted cell, including RPE cells themselves. Applicants argument is not persuasive because the citation does not state the RPE cells are allogenic to the mammal as claimed. Claim 12 as originally filed does not support the phrase because it does not state the RPE cells are allografts or allogenic to the mammal as claimed. Instead, the specification states the cells being administered with the RPE are allogeneic (pg 7, line 26).

Deletion of “allogeneic” describing the non-RPE in claim 56, 62 and 72 as amended is new matter. The specification does not contemplate combining RPE with any insulin-producing, non-RPE as broadly amended. Applicants do not point to support for the amendment and support cannot be found. The specification teaches combining RPE and insulin-producing β -cells (pg 4, line 33) or pancreatic islet of Langerhans cells (claim 22 as originally filed) which does not support combining RPE with any insulin-producing, non-RPE as broadly claimed.

2. Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administering a

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composition to mammal, said composition comprising retinal pigmented epithelial cells (RPE) and non-RPE, wherein said non-RPE cells are allogeneic to said mammal, does not reasonably provide enablement for increasing survival of the non-RPE in the mammal, producing a therapeutic protein/biologically active molecule by administering the non-RPE or obtaining a therapeutic effect by administering the non-RPE. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

The invention relates to administering allogeneic cells to a mammal using RPE such that an immune privileged site is obtained, protecting the non-RPE from the immune system of the mammal. The only disclosed purpose for administering the allogeneic cells is to treat disease by obtaining therapeutic levels of a biological molecule secreted by the allogeneic cells (pg 4, line 20).

The state of the art at the time of filing was that symptoms of Parkinson's disease were treated using RPE cells supported by a matrix transplanted into the brain of rats (Cherksey, see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). Cherksey did not expressly teach co-administering RPE and non-RPE cells, wherein the non-RPE were allogeneic to the host. However, Cherksey suggests transplanting a matrix having both RPE and allogeneic glial cells (column 9, line 2; column 11, line 37).

In addition, the art at the time of filing taught administering non-RPE into mammals to produce therapeutic molecules (Sigalla of record, Sept. 1, 1997, Human Gene Therapy, Vol. 8,

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pages 1625-1634; page 1626, column 2, 2nd and 3rd paragraphs; page 1628, column 1, 4th paragraph and column 2, 4th and 5th full paragraphs; Weber of record, 1997, *J. Surg. Res.*, Vol. 69, pages 23-32; page 25, column 1, "Islet transplantation"; page 27, paragraph bridging columns 1 and 2; Fraser of record, 1995, *Cell Transplantation*, Vol. 4, pages 529-534).

While RPE were known to provide "immune privilege" (Ye of record, 1993, *Current Eye research*, Vol. 12, pages 629-639, see page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20), the art at the time of filing did not teach the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal, define the immune response to such a site or teach how to increase survival of allogeneic non-RPE in a mammal using RPE. Therefore, it was unpredictable at the time of filing how to increase survival of allogeneic non-RPE in a mammal using RPE as claimed. Nor did the art at the time of filing teach how to obtain therapeutic levels of biological molecules produced by non-RPE protected within an immune privileged site created by RPE. Therefore, it was also unpredictable at the time of filing how to obtain therapeutic secretion of biological molecules produced by non-RPE protected within RPE cells.

The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE *in vitro* (pages 21-27). The specification suggests treating a number of diseases (page 1, line 23; page 3, line 26; page 5, line 31), delivering RPE to any of a number of tissues (page 15, line 7), administering RPE and non-RPE as a single composition or as separate compositions (page 4, line

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23) and using non-RPE such as neural cells, endocrine cells, muscle cells and other cells that produce a functionally active therapeutic molecule (sentence bridging pages 6 and 7). The specification does not teach administering RPE and non-RPE to a mammal, obtaining a therapeutic effect by administering RPE and allogeneic non-RPE or increasing the survival time of allogeneic non-RPE using RPE.

However, the specification does not enable administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal such that survival of the graft is facilitated or such that a therapeutic effect is obtained as claimed. A mere suggestion to increase the survival of allogeneic cells or to treat disease in a mammal by administering the allogeneic cells in combination with RPE is inadequate to overcome the unpredictability in the art to use the claimed invention to increase the survival of the non-RPE or to treat disease. The specification does not teach the structure obtained upon administering RPE and non-RPE, the immune response to such a site, the level of secretion of molecules produced by the non-RPE, or treating disease using such a method. The specification does not teach the immune response to such a site or rate of survival of the allogeneic non-RPE cells. The specification does not teach administering RPE and non-RPE to a mammal, wherein the non-RPE are allogeneic to the mammal. Therefore, the specification does not overcome the unpredictability in the art by teaching how to use RPE and allogeneic non-RPE to increase survival of the non-RPE or to secrete therapeutically effective amounts of a biologically active molecule from non-RPE in such a site.

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Specifically, the specification does not provide any guidance on how to use allogeneic pancreatic islet of Langerhans cells (claims 57, 63, 73) or insulin-producing cells (claim 56, 62, 72) in combination with RPE to treat disease for reasons of record.

Applicants point to pg 16-28, which are described above along with a discussion of why the examples do not correlate to the claims or provide adequate guidance for one of skill to increase survival of allogeneic, non-RPE or to treat disease. Applicants arguments do not discuss how the examples on pg 16-28 correlate to the claims or why the rejection is misplaced. Therefore, applicants arguments are not persuasive.

Applicants point to pg 6-7 which describes examples of non-RPE that may be administered with RPE and is discussed above. Applicants argument is not persuasive because applicants do not discuss how merely listing potential non-RPE is adequate to overcome the unpredictability established above.

Applicants point to pg 8, lines 16-20, which describes examples of RPE cells that may be used in the invention. Applicants point to pg 15-16 which describes methods of administering the cells of the invention, dosages of RPE cells, states administration is accomplished by conventional techniques, and methods of assessing the immune response. Applicants conclude that the disclosure is adequate for one of skill in the art to practice the invention without undue experimentation. Applicants arguments are not persuasive. The teachings in the specification are not adequate to increase survival of the allogeneic, non-RPE cells because they do not teach the structure of a site resulting from administering RPE and allogeneic non-RPE to a mammal, define

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the immune response to such a site such that increased survival of the non-RPE could be expected or provide a reasonable correlation between the conventional methods of administering cells and dosages or types of cells listed are adequate to overcome the unpredictability in the art such that increased survival of allogeneic, non-RPE in a mammal could be obtained using RPE. The teachings in the specification are not adequate to use the claimed invention to treat disease because the specification does not provide any indication that therapeutic levels of biological molecules can be secreted by allogeneic, non-RPE protected within an immune privileged site created by RPE.

Applicants argue Selawry (1993, Cell Trans., Vol. 2, pg 123) and Selawry (US Patent 5,725,854) support the claimed invention because they teach administering sertoli cells and pancreatic islet cells such that the sertoli cells create an immune-privileged site and the islet cells produce therapeutic levels of a biological molecule. Applicants argument is not persuasive. The specification does not provide adequate correlation between Sertoli cells and RPE such that similar results could be obtained. It cannot be determined if Sertoli cells and RPE create an immune privileged site by the same means, if both Sertoli cells and RPE secrete FasL, if the structure of the site created by Sertoli cells and RPE is the same, if biological molecules secrete through a structure created by RPE or that the amount of secretion obtained using RPE cells would be equivalent to that observed using Sertoli cells.

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3. Claims 41, 42, 44-46, 48-50, 55-57, 62, 63, 65, 66 and 68-73 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 65 remains indefinite because the preamble of the claim is not commensurate in scope with the body of the claim. The phrase "facilitating survival of an allogeneic graft" has a different scope than "increasing survival time" of cells that are allogeneic to the mammal. It appears that the preamble is intended to increase the survival time of all allogeneic cells that are administered to the host; however, the body of the claim only requires increasing the survival of the non-RPE cells. Changing "facilitating survival of an allogeneic graft of a population of non-RPE cells" to --increasing survival of a population of non-RPE cells-- in the preamble and changing "increasing survival time of the allogeneic graft of the population of non-RPE cells in the mammal" to --increasing survival of the population of non-RPE cells in the mammal-- in the body of the claim would overcome this rejection. If the suggested changes to claim 65 are made, dependent claims should be amended as necessary to reflect the language of claim 65. Applicants have not addressed this rejection.

Claim 65 remains indefinite because it is unclear to what the survival time of the population of non-RPE cells is being compared. Is the survival time greater in the mammal than *in vitro*? greater in the mammal using RPE as compared to administering the non-RPE cells alone? greater than administering autologous non-RPE? As such the metes and bounds of when increased survival time of the non-RPE has been obtained cannot be determined. Overall, the

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result of administering RPE and non-RPE still cannot be determined. Applicants have not addressed this rejection.

Claim Rejections - 35 USC § 103

4. Claims 41, 42, 44-46, 48, 49, 65 and 68-73 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record.

Cherksey taught treating symptoms of Parkinson's disease using 300-3.75x10⁵ RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24). RPE cells inherently secrete FasL and create localized immunosuppression (pg 2, line 27, of the specification). Cherksey does not teach co-administering RPE and non-RPE cells. However, Cherksey suggests transplanting a matrix having both RPE and glial cells attached (column 9, line 2) and that the glial cells may be allogeneic to the host (column 11, line 37). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer RPE and glial cells wherein the glial cells are allogeneic to the host as taught by Cherksey. One of ordinary skill in the art at the time the invention was made would have been motivated to add glial cells to the RPE as suggested by Cherksey and to treat neural disorders in the brain. The method of Cherksey increases "survival time" of the glial cells as compared to leaving the glial cells on the counter. The method of Cherksey increases "survival

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time" of the glial cells as compared to administering allogeneic glial cells without RPE because RPE inherently secrete FasL causing an "immune privilege site." Case law established that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Applicants argue that Cherksey does not teach RPE cells secrete FasL to create localized immunosuppression. Therefore, applicants argue Cherksey does not teach all the limitations of the claims. Applicants argument is not persuasive. RPE cells inherently secrete FasL and created localized immunosuppression (pg 2, line 27). Cherksey need not teach the inherent feature of the RPE cells as claimed. Case law established that reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Claim 50 appears to be free of the prior art of record because the prior art of record does not teach or suggest administering RPE and non-RPE separately in an amount effective to sustain a therapeutic effect. Claims 56, 57, 62, 63, 72 and 73 appear to be free of the prior art of record because the prior art of record did not teach or suggest combining RPE and insulin-producing cells such as pancreatic islet of Langerhans cells as claimed. Claim 66 appears to be free of the prior art of record because the prior art of record did not teach or suggest administering RPE and non-RPE to a mammal, wherein both the RPE and non-RPE are allogeneic to the mammal.

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Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER